

THE ACTION OF *URGINEA BURKEI* (BAKER).

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Urginea Burkei (Baker), a plant of the Natural Order of *Liliaceae* more commonly known as the Transvaal slang-kop, is responsible for many fatal cases of poisoning among sheep and other stock in certain parts of Africa. Poisoning is usually due to animals eating the young shoots and leaves. The symptoms are vomiting and diarrhoea, and, in fatal cases, paralysis and coma. Several investigators have recorded similar effects when animals are fed experimentally with the bulb, but I am unaware of any experimental work done to test the precise pharmacological action of the drug. The present research was performed to elucidate this action.

In the experiments to be described I used preparations from the bulb, for a supply of which I am indebted to Dr C. F. Juritz, of the Agricultural Research Department. I have not yet been able to obtain any of the leaves.

PART I.—EXPERIMENTAL.

A. PREPARATION OF TINCTURE AND EXTRACT.

The dried bulb was powdered, macerated in 60 per cent. alcohol for three days, and then strained through three folds of linen. The marc was percolated with two further lots of 60 per cent. alcohol.

The extract was prepared from the tincture by heating it to dryness over a water-bath.

In the experiments, except where stated, a tincture, of which 10 c.c. were equivalent to 1 gm. of the dried bulb, and an extract, of which 1 gm. was equivalent to 5.93 gm. of the bulb, were used. No attempt was made to isolate any pure principle.

B. LOCAL ACTION.

The powdered bulb is very irritating, and inhalation of small quantities produced sneezing, lachrymation and coughing.

A solution of the extract applied to the frog's mesentery induced a marked inflammatory reaction in a few minutes.

Administration of 0.1 gm. of the extract to a cat through a stomach-tube was followed by vomiting and diarrhoea. Inflammation of the stomach and intestine was found on post-mortem examination.

C. GENERAL ACTION.

The general action is seen best when subcutaneous injections of a solution of the drug are given to frogs or mammals. In many cases when it was administered by mouth the local action on the gastro-intestinal tract was seen, but no other action. The reason of the comparative inability of the extract to produce general symptoms in such cases may be: (i) Loss of the greater portion in the vomit; (ii) destruction of the active ingredient by the digestive juices; or (iii) very slow absorption.

(a) *General Action on Frogs.*

About fifty experiments were done, and all gave similar results. The following is a typical example:

Frog, *Rana platana*, male, weight 65 grm.

11 a.m.: 3.25 mgrm. of extract of *Urginea Burkei* dissolved in 0.5 c.c. of Ringer's solution injected into anterior lymph-sac of thigh.

11.5 a.m.: Frog has been jumping about and showing signs of increased activity.

11.15 a.m.: Spontaneous movements have ceased. Frog lies passive, with fore limbs extended by side and hind limbs flexed at every joint. Able to turn over if laid on back. Reflexes greatly diminished.

11.35 a.m.: No power of movement. Respirations very slow.

12.5 p.m.: Chest opened. Heart very slow. Auricles beating twice for one beat of ventricle. Apex of ventricle pale.

12.15 p.m.: Heart has ceased to beat. Ventricle pale and contracted; auricles engorged and distended. The gastrocnemius muscle responds to direct stimulation and to stimulation of the sciatic nerve.

Variations.—The diminution of conductivity, resulting in failure of alternate impulses to pass from auricle to ventricle, was seen in about one-third of the cases. In several experiments the ventricle stopped in diastole or only partial systole, but a slight mechanical stimulus applied to the ventricle was sufficient to send it into complete systole.

(b) *Dose to produce Systolic Arrest in One Hour.*

Method.—A tincture was used in which 5 c.c. were equivalent to 1 grm. of the bulb. Most of the alcohol was driven off by gentle heat and the tincture made up to the original bulk with Ringer's solution. A measured amount of this was made up to 0.5 c.c. with Ringer's solution and injected into the ventral lymph-sac of a frog. At the end of one hour the frog was pithed and the heart examined.

Results.—Twenty-four experiments with varying doses were made, and it was found that the dose required to produce systolic arrest in one hour was 0.006 c.c. of 20 per cent. tincture per gramme of body-weight of frog. It is

noteworthy that in many cases at the end of the hour there was little evidence of loss of power in the frog's muscles, but the cardiac action was well developed.

The frogs used were the South African variety, *Rana platana*. They were treated with strophanthin that had been used in England on *Rana temporaria*. The English and South African frogs required the same dose per gramme of strophanthin to produce systolic arrest of the heart.

(c) *General Action on Mammals.*

In thirty-eight experiments the tincture or extract of *Urginea Burkei*, dissolved in Ringer's solution, was injected subcutaneously into rats, rabbits and cats.

A few minutes after injection of a lethal dose the respirations were greatly accelerated, and there was, as a rule, profuse salivation. The animal soon began to sway from side to side and to drag its hind legs when walking. The muscular weakness progressed, and soon afterwards the animal lay down on its side apparently quite powerless. The respiration was slow, and, in many cases, irregular and gasping. Coma developed, in a few instances preceded by convulsions, and a few minutes afterwards the heart and respiration ceased. No vomiting occurred, but three animals made retching movements.

Sublethal doses produced symptoms of less severity. A dose less than one-third of the minimal lethal dose was followed by depression or salivation, or had no apparent effect.

The frequent occurrence of vomiting when the drug was given by mouth, and its absence when intravenous or subcutaneous injections were made, would point to the chief cause of vomiting being reflex from irritation of the stomach.

(d) *Minimal Lethal Dose for Rat and Rabbit.*

The minimal lethal dose of the extract for the rabbit by subcutaneous injection is 0.025 gm. per kilogramme of body-weight, and for the rat 0.4 gm. The rat therefore has a certain degree of natural tolerance for the poison as compared with the rabbit, the minimal lethal dose being sixteen times as great.

D. ACTION ON THE CIRCULATORY SYSTEM.

(a) *Action on the Isolated Frog's Heart.*

The contractions of the isolated frog's heart were recorded by perfusion through a cannula tied into the inferior vena cava. A second cannula was inserted into the left branch of the aorta and all the other vessels were tied. Ringer's solution was perfused until the heart became regular, then a solution of the tincture or extract was perfused.

The first effect is an increase in the extent of systole. Very soon the rhythm of the heart is slowed. The output per minute, measured by the outflow from the aortic cannula, is increased. The slowing becomes more marked, and after some time the relaxation of the ventricle is impaired and the output of the heart decreases. These changes continue, gradual increase in the contraction and slowing and diminution in the diastolic relaxation and outflow, until the heart is finally arrested in complete systole.

Fig. 1 shows the effect of perfusing the isolated frog's heart with 1 in 5000 extract of *Urginea Burkei*. A is the normal heart-beat. B to H are the effects produced at three-minute intervals after perfusion. The heart is stopped in 21 minutes in systole.

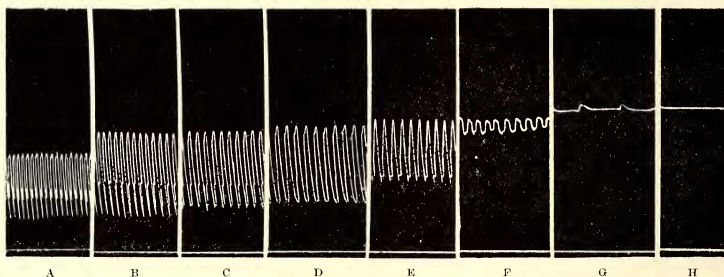


FIG. 1.

(b) *Action on the Frog's Heart in situ.*

The tracings obtained from the frog's heart *in situ* were practically a reproduction of those obtained from the isolated heart. With sufficient dosage there was stoppage of the heart, the ventricle in systole and the auricles in diastole.

(c) *Action on the Isolated Mammalian Heart.*

Rabbits, cats, rats and guinea-pigs were used in the experiments. The animal was killed and the heart quickly removed. A cannula was inserted into the aorta and the heart perfused through the coronary arteries with oxygenated Locke's solution at 37° C. The tip of the ventricle was attached to a lever writing on a smoked drum.

The first effects noticeable on adding tincture or extract of slang-kop to the perfusing fluid are increase in systole and diastole and slight slowing. The subsequent events follow one of three courses: (1) The heart remains slow but regular; the extent of systole increases, while that of diastole, after the preliminary increase, decreases until the heart is arrested in systole like

the frog's heart. Fig. 2 shows the effect of perfusing the cat's heart with 1 in 200 tincture of *Urginea Burkei*. The upstroke denotes systole. A is the normal heart-beat. B to J show the effect on the heart when the experimental solution has perfused for 1, 2, 3, 5, 7, 9, 10, 11 and 12 minutes respectively. This is the most characteristic action of slang-kop on the mammalian heart.

(2) Heart-block may appear. This may be sinu-auricular, the heart suddenly beating at half its previous rate, but is more commonly auriculo-ventricular, the ventricle beating at a slower rate than the auricle. Very soon the block becomes complete, no impulse passing from auricle to ventricle. In these cases it is noticeable that the tone of the ventricle increases as the drug is perfused, even after pulsations have ceased, and it soon is firmly contracted.

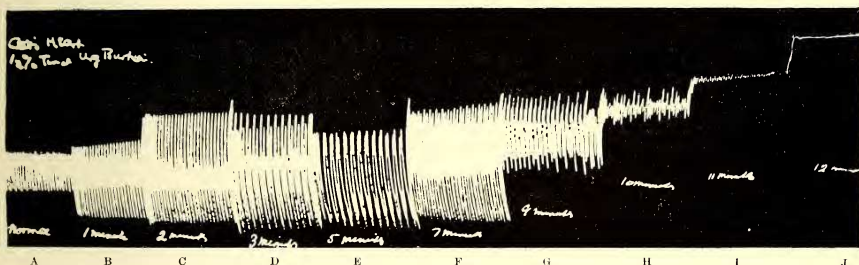


FIG. 2.

(3) The heart after the preliminary slowing may become quick and irregular. Pulsus alternans and extra-systoles appear. These rarely pass off, but if they do the heart may finish as in (1) or (2). More commonly however, the extra-systoles are the precursors of fibrillation of the auricles and ventricles, and the heart ceases after a short period of extreme irregularity.

The rat's heart is less susceptible to the action of the poison than the cat's or rabbit's heart.

(d) Action on the Mammalian Heart in situ.

Method.—The animal—rabbit or cat—was anaesthetised with paraldehyde or urethane followed by ether. Cannulae were inserted into the trachea, left carotid artery and right jugular vein. Artificial respiration was commenced and the thorax opened in the middle line. A cardiometer, connected by rubber tubing to a recording tambour, was placed round the heart and the

pericardium tied round it. The rate and volume of the heart were thus recorded.

Results.—With small doses the heart is slowed and systole increased, and the heart empties itself more completely at each beat. With fatal doses the slowing is very transient and soon gives place to quickening and irregularity, with onset of fibrillation and arrest of the heart in one or two minutes. In one case well-marked heart-block was seen. The action of slang-kop on the mammalian heart *in situ* differs from its action on the frog's heart and also the isolated mammalian heart in that the heart *in situ* is arrested in diastole. The preliminary slowing has a different cause from the slowing seen in the isolated mammalian heart, which can only be due to an action of the drug on the heart itself or the vagus terminations in the heart. The slowing in the intact animal is not seen if the vagi nerves be cut, and is therefore due to direct stimulation of the vagus centre by the

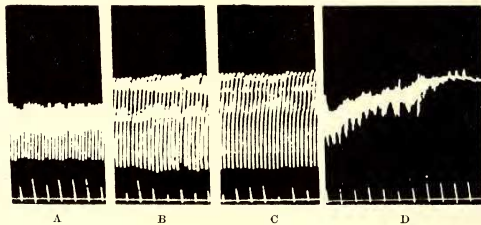


FIG. 3.

toxic substance, or to indirect stimulation following the rise of blood-pressure as in the case of adrenalin. Fig. 3 shows the movements of the heart of a cat (weighing 2340 grm.), recorded with the cardiometer. The downstroke denotes systole. A is the normal heart-beat. B shows the movements one minute after injecting 0.5 c.c. of tincture of *Urginea Burkei* into the jugular vein: the heart is slowed, and systole and diastole are increased. C shows the effect at the end of two minutes. D shows the terminal fibrillation, beginning in three minutes, and arrest of the heart in diastole in less than four minutes.

(e) *Effect on Blood-pressure.*

In most of the experiments the blood-pressure from the carotid artery and the heart-volume, as shown by the cardiometer, were recorded simultaneously. After injection of slang-kop there is a large and persistent rise of blood-pressure, commonly equal to 50 or 60 mm. of mercury, but sometimes much more. With the onset of irregularity the blood-pressure falls.

Fig. 4 shows a rise of pressure of 120 mm. after injection of 0.5 c.c. of tincture of *Urginea Burkei* into the jugular vein of a cat weighing 4350 grm.

(f) Action on Blood-vessels.

The volume of an isolated loop of intestine was recorded with the plethysmograph, as shown in Fig. 5; the line i-v denotes intestinal volume.

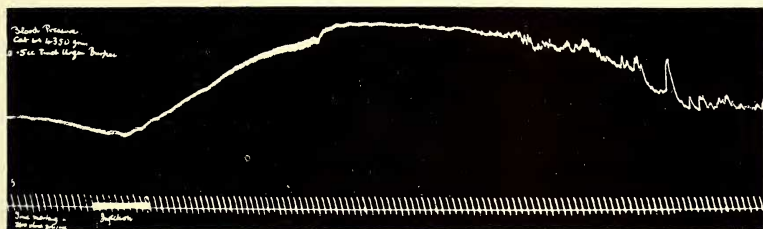


FIG. 4.

Injection of 0.5 c.c. of tincture in this case causes a rise of blood-pressure of 30 mm. This is accompanied by a decrease in the intestinal volume, indicating constriction of the vessels. A second injection produces a similar result. (The constriction is not as great as the tracing would appear to show, as the movement of the lever was magnified thirty times, and the tambour was small.) The action is on the vessel-wall, as it is still seen after the autonomic nerve-endings are paralysed with a preliminary injection of ergotoxine.

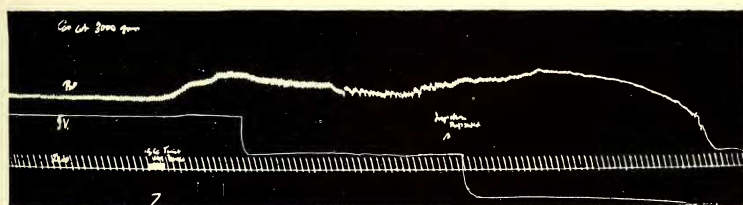


FIG. 5.

The effect on the coronary arteries was much less pronounced, and with small concentrations the vessels were dilated and the outflow increased.

E. EFFECT ON THE KIDNEY SECRETION.

The diuretic action was studied by measuring the flow of urine from the ureters of rabbits, before and after administration of the drug. Small doses

almost invariably caused an increase of urine, but large doses caused a decrease, in a few cases preceded by a slight augmentation of the flow. It is probable that the urine is diminished in those cases where the renal vessels are so constricted as to impair the blood-supply of the kidney.

F. ACTION ON UNSTRIPED MUSCLE.

The movements of the isolated uterus and intestine of the cat and rabbit were augmented by 1 in 500 tincture of slang-kop.

PART II.—DISCUSSION.

From these results it will be seen that the action of *Urginea Burkei* is the same as that of the digitalis group of bodies. This group includes a number of substances of great medicinal value, the most important being digitalis, strophanthus and squill.

Squill is obtained from *Scilla maritima*, a plant of the same natural order as, and of similar appearance to, slang-kop. The action of the two plants is almost identical, and the toxicity to the frog is the same. Slang-kop would seem to be slightly more toxic to mammals. It is possible that *Urginea Burkei* might replace squill in South Africa, and in fact it may be found superior. How far the action is produced when slang-kop is given by mouth must be determined, and this is being investigated further.

I beg to thank the Advisory Board of Industry and Science for bringing this subject to my notice as one suitable for research.

SUMMARY.

The results of a large number of experiments show that *Urginea Burkei* (Baker), the Transvaal slang-kop, has the same actions as the digitalis bodies, and suggest its possible use as a South African substitute for squills.